

## REMARKS

### Formal Matters

The title has been amended to more distinctly describe the invention.

The specification has been amended to update the cross-reference information on page 1 of the specification, to replace the term "Lyspro" with the term "insulin lispro" in paragraphs 0058 and 00172, and to correct typographical errors in paragraphs 0050 and 00209. Claims 21-31 have been cancelled and new claims 32-52 have been added.

Claims 32-52 are now pending after entry of the amendments set forth herein.

A clean version of the specification has been provided as a separate document accompanying this Amendment. A clean version of the new claims 32-52 is provided above. A marked-up version of the changes made to the specification and claims by this amendment is attached hereto and captioned "Version with Markings to Show Changes Made".

No new matter has been added by the above mentioned amendments.

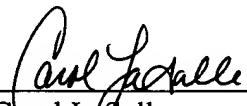
### Conclusion

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number AERX058CON3.

Respectfully submitted,  
BOZICEVIC, FIELD & FRANCIS LLP

Date: 5/3/01

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

In the Title:

The title has been amended to read -- A METHOD OF TREATING DIABETES MELLITUS IN A PATIENT--.

In the Specification:

The specification has been amended as follows:

On page 1, after "CROSS-REFERENCES" starting at line 6 as follows:

This application is a continuation of Application Serial No. 09/686,212, filed October 10, 2000, which is a continuation of Application Serial No. 09/378,638, filed August 20, 1999 and issued as U.S. Patent No. 6,167,880 on January 2, 2001, which is a divisional [application] of Application Serial No. 09/160,909, filed September 25, 1998 and issued as U.S. Patent 5,941,240 on August 24, 1999, which is a continuation of Application Serial No. 08/846,243 filed April 25, 1997 and issued as U.S. Patent 5,[99]884,620 on March 23, 1999, which is a continuation-in-part of Application Serial No. 08/754,423 filed November 22, 1996 and issued as U.S. Patent 5,743,250 on April 28, 1998, which is a continuation-in-part of Application Serial No. 08/549,343, filed on October 27, 1995 and issued as U.S. Patent No. 5,915,378 on June 29, 1999, which is a continuation-in-part of Application Serial No. 08/331,056, filed on October 28, 1994 and issued as U.S. Patent No. 5,672,581 on September 30, 1997, which is a continuation-in-part of Application Serial No. 08/011,281, filed on January 29, 1993 and issued as U.S. Patent 5,364,838 on November 15, 1994, each of which is incorporated herein by reference and to which is claimed priority under 35 USC §120.

On page 9 at paragraph 0050 as follows:

FIG. 11 is a graph showing a [focussed] focused area of the graph of FIG. 10;

On page 11 at paragraph 0058 as follows:

The term "insulin analog" is intended to encompass any form of "insulin" or defined above including forms wherein one or more of the amino acids within the polypeptide chain has been replaced with an alternative amino acid and/or wherein one or more of the amino acids has been deleted or wherein one or more additional amino acids has been added to the polypeptide chain. In general, the "insulin analogs" of the present invention include "super insulin analogs" wherein the ability of the

insulin analog to affect serum glucose levels is substantially enhanced as compared with conventional insulin as well as hepatoselective insulin analogs which are more active in the liver than in adipose tissue. Analogs include insulin-like compounds used for the same general purpose as insulin such as insulin lispro [Lyspro] i.e., compounds which are administered to reduce blood glucose levels.

On page 47 at paragraph at 00172 as follows:

Other than insulin lispro [Lyspro], the insulin analogs are not presently used for the treatment of patients on a commercial scale. However, insulin lispro and other insulin analogs being developed could be used with the present invention in that the present invention can be used to provide variable dosing in response to currently measured serum glucose levels. Further, since many insulin analogs are more potent than conventional insulin, their delivery via the intrapulmonary route is particularly convenient.

On page 57 at paragraph 00209 as follows:

After an aerosolized dose of insulin has been produced and inhaled into the patient's lungs the inhale-exhale maneuver can be performed at any time. Performing the maneuver provides advantages in that it increases the rate at which the insulin enters the circulatory system and thereby makes it possible to more accurately control the amount of additional insulin the patient might need in order to properly adjust the glucose level. If the maneuver is to be performed a greater amount of time must pass until the patient is sure that sufficient insulin has not already been absorbed. Regardless of the manner by which the insulin is administered i.e., by injection or inhalation there is some lag time between the administration of a dose of insulin and its effect on the serum glucose level. Thus, regardless of the means of administration and even when the inhale-exhale maneuver is performed some time must be allowed to pass for the glucose level to decrease prior to the administration of additional insulin in order to avoid overdosing. The use of the inhale-exhale maneuver decreases the "lag" time which is already decreased due to intrapulmonary administration as compared to subcutaneous injections. Further, as indicated above, the microprocessor can be programmed to prevent overdoses.

In the claims:

32. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) supplying a predetermined amount of insulin to a hand held device, said predetermined amount being in excess of that amount required, in the bloodstream of said patient, to produce or

maintain an acceptable serum glucose level in said patient;

(b) contacting said insulin with a compressed gas to form a cloud in said hand held device, said cloud comprising a repeatable amount of insulin, said repeatable amount being in excess of that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient, wherein an amount of said insulin in said cloud effective, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient is absorbed into the bloodstream of said patient.

33. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) supplying a predetermined amount of insulin to a hand held device, said predetermined amount being in excess of that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient;

(b) contacting said insulin with a compressed gas to form a cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being in excess of that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient, wherein an amount of insulin in said cloud effective, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient is absorbed into the bloodstream of said patient.

34. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) mechanically supplying a predetermined amount of insulin to a given area of a hand held device, said predetermined amount being in excess of that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient;

(b) aerosolizing said insulin with a compressed gas to form a cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being in excess of that amount required, in the bloodstream of said patient, to produce or

maintain an acceptable serum glucose level in said patient; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient, wherein an amount of insulin in said cloud effective, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient is absorbed into the bloodstream of said patient.

35. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) supplying a predetermined amount of insulin in the form of a dry powder to a hand held device, said predetermined amount being in excess of that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient;

(b) contacting said insulin with a compressed gas to form a cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being in excess of that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient, wherein an amount of insulin in said cloud effective, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient is absorbed into the bloodstream of said patient.

36. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) mechanically supplying a predetermined amount of insulin in the form of a dry powder to a given area of a hand held device, said predetermined amount being in excess of that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient;

(b) aerosolizing said insulin with a compressed gas to form a cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being in excess of that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient, wherein an amount of insulin in said cloud effective, in the

bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient is absorbed into the bloodstream of said patient.

37. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) supplying a predetermined amount of insulin in the form of a dry powder to a hand held device, said predetermined amount being 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in the blood of said patient;

(b) contacting said insulin with a compressed gas to form a dry cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in the blood of said patient; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient, wherein an amount of insulin in said cloud effective, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient is absorbed into the bloodstream of said patient.

38. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) mechanically supplying a predetermined amount of insulin in the form of a dry powder to a given area of a hand held device, said predetermined amount being 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient;

(b) aerosolizing said insulin with a compressed gas to form a dry cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in the blood of said patient; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient, wherein an amount of insulin in said cloud effective, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient is absorbed into the bloodstream of said patient.

39. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) supplying a predetermined amount of insulin in the form of a dry powder to a hand held device, said predetermined amount being 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient;

(b) contacting said insulin with a compressed gas to form a dry cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in the blood of said patient; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient, wherein 1 to 30 units of insulin are absorbed into the bloodstream of said patient.

40. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) mechanically supplying a predetermined amount of insulin in the form of a dry powder to a given area of a hand held device, said predetermined amount being 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient;

(b) aerosolizing said insulin with a compressed gas to form a dry cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in the blood of said patient; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said insulin cloud to the lungs of said patient, wherein 1 to 30 units of insulin are absorbed into the bloodstream of said patient.

41. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) supplying a predetermined amount of insulin in the form of a dry powder to a hand held device, said predetermined amount being 2 to 300 units of insulin;

(b) contacting said insulin with a compressed gas to form a dry cloud in said hand held

device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being 2 to 300 units of insulin; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient; wherein 1 to 30 units of insulin are repeatably absorbed into the bloodstream of said patient.

42. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) mechanically supplying a predetermined amount of insulin in the form of a dry powder to a given area of a hand held device, said predetermined amount being 2 to 300 units of insulin;

(b) aerosolizing said insulin with a compressed gas to form a dry cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being 2 to 300 units of insulin; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient; wherein 1 to 30 units of insulin are repeatably absorbed into the bloodstream of said patient.

43. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) determining the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level;

(b) aerosolizing, in a hand held device, a predetermined amount of insulin in excess of said required amount of insulin with a compressed gas to form a cloud in said hand held device, said cloud comprising a repeatable amount of insulin in excess of said required amount of insulin; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said insulin cloud to the lungs of said patient, wherein said required amount of insulin is absorbed into the bloodstream of said patient.

44. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) determining the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable blood glucose level;



(b) aerosolizing, in a hand held device, a predetermined amount of insulin in excess of said required amount of insulin with a compressed gas to form a cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin in excess of said required amount of insulin; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient, wherein said required amount of insulin is absorbed into the bloodstream of said patient.

45. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) determining the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level;

(b) aerosolizing, in a hand held device, a predetermined amount of insulin 2 to 10 times said required amount of insulin with a compressed gas to form a dry cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being 2 to 10 times said required amount of insulin; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient, wherein said required amount of insulin is absorbed into the bloodstream of said patient.

46. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) determining the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level, said required amount being 1-30 units;

(b) aerosolizing, in a hand held device, a predetermined amount of a dry powder comprising insulin, said predetermined amount being 2 to 10 times said required amount of insulin, with a compressed gas to form a dry cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being 2 to 10 times said required amount of insulin; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said cloud to the lungs of said patient, wherein from 1 to 30 units of insulin are absorbed into the bloodstream of said patient.

47. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) determining the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level, said required amount being from 1-30 units;

(b) aerosolizing, in said hand held device, a predetermined amount of insulin in the form of a dry powder, said predetermined amount being from 2 to 300 units of insulin, with a compressed gas to form a dry cloud in said hand held device, said cloud comprising a repeatable and controlled amount of insulin, said repeatable and controlled amount being from 2 to 300 units of insulin; and

(c) inhaling said cloud at an inspiratory flow rate and volume adapted to deliver a portion of said insulin cloud to the lungs of said patient; wherein from 1 to 30 units of insulin are repeatably absorbed into the bloodstream of said patient.

48. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) aerosolizing, in a hand held device, a first predetermined amount of insulin, which is in excess of the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level, with a compressed gas to form a first cloud in said hand held device, said first cloud comprising a first repeatable and controlled amount of insulin which is in excess of the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level;

(b) inhaling said first cloud at an inspiratory flow rate and volume adapted to deliver a portion of said first cloud to the lungs of said patient, wherein insulin is absorbed into the bloodstream of said patient; and

(c) repeating (a) and (b) with a second predetermined amount of insulin which is the same as or different from said first predetermined amount and is in excess of the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level and a second repeatable and controlled amount of insulin which is the same as or different from said first repeatable and controlled amount and is in excess of the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level.

49. (New) A method of treating diabetes mellitus in a patient in need thereof, said method

comprising:

(a) aerosolizing, in a hand held device, a first predetermined amount of insulin in the form of a dry powder with a compressed gas to form a first cloud in said hand held device, said first predetermined amount being an amount in excess of the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level, said first cloud comprising a first repeatable and controlled amount of insulin which is in excess of the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level;

(b) inhaling said first cloud at an inspiratory flow rate and volume adapted to deliver a portion of said first cloud to the lungs of said patient, wherein insulin is absorbed into the bloodstream of said patient; and

(c) repeating (a) and (b) with a second predetermined amount of insulin which is the same as or different from said first predetermined amount and is in excess of the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level and a second repeatable and controlled amount of insulin which is the same as or different from said first repeatable and controlled amount and is in excess of the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level.

50. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) aerosolizing, in a hand held device, a first predetermined amount of insulin in the form of a dry powder, said first predetermined amount being 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient, with a compressed gas to form a first dry cloud in said hand held device, said first cloud comprising a first repeatable and controlled amount of insulin which is 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient;

(b) inhaling said first cloud at an inspiratory flow rate and volume adapted to deliver a portion of said first cloud to the lungs of said patient, wherein insulin is absorbed into the bloodstream of said patient;

(c) repeating (a) and (b) with a second predetermined amount of insulin which is the same as or different from said first predetermined amount and is in excess of the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level and a second repeatable and controlled amount of insulin which is the same as or different from said first repeatable

and controlled amount and is in excess of the amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level.

51. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) aerosolizing, in a hand held device, a first predetermined amount of insulin in the form of a dry powder, said first predetermined amount being 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient, with a compressed gas to form a first dry cloud in said hand held device, said first cloud comprising a first repeatable and controlled amount of insulin which is 2 to 10 times that amount required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level in said patient;

(b) inhaling said first cloud at an inspiratory flow rate and volume adapted to deliver a portion of said first cloud to the lungs of said patient, wherein 1 to 30 units of insulin are absorbed into the bloodstream of said patient;

(c) repeating (a) and (b) with a second predetermined amount of insulin which is the same as or different from said first predetermined amount and is 2 to 10 times that amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level and a second repeatable and controlled amount of insulin which is the same as or different from said first repeatable and controlled amount and is 2 to 10 times that amount of insulin required, in the bloodstream of said patient, to produce or maintain an acceptable serum glucose level.

52. (New) A method of treating diabetes mellitus in a patient in need thereof, said method comprising:

(a) aerosolizing, in a hand held device, a first predetermined amount of insulin in the form of a dry powder, said first predetermined amount being 2 to 300 units of insulin, with a compressed gas to form a first dry cloud in said hand held device, said first cloud comprising a first repeatable and controlled amount of insulin being 2 to 300 units of insulin;

(b) inhaling said first cloud at an inspiratory flow rate and volume adapted to deliver a portion of said first cloud to the lungs of said patient; wherein from 1 to 30 units of insulin are repeatably absorbed into the bloodstream of said patient;

(d) repeating (a) and (b) with a second predetermined amount which is the same as or different from said first predetermined amount and is 2 to 300 units of insulin and a second repeatable

and controlled amount which is the same as or different from said first repeatable and controlled amount and is 2 to 300 units of insulin.

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